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Smit, Renata; Postma, Maarten J

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Renata Šmit & Maarten J Postma

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# Vaccines for tick-borne diseases and cost-effectiveness of vaccination: a public health challenge to reduce the diseases' burden

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**Renata Šmit**

Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), University of Groningen, Groningen, Netherlands and Institute of Science Healthy Aging & healthcARE (SHARE), University Medical Center Groningen (UMCG), Groningen, Netherlands  
Author for correspondence:  
Tel.: +386 143 611 05  
[renata\\_smit@t-2.net](mailto:renata_smit@t-2.net)



**Maarten J Postma**

Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), University of Groningen, Groningen, Netherlands Institute of Science Healthy Aging & healthcARE (SHARE), University Medical Center Groningen (UMCG), Groningen, Netherlands

Tick-borne encephalitis (TBE) and Lyme borreliosis (LB) are tick-borne diseases (TBDs), and both present an increasing burden worldwide. Vaccination as public health intervention could be the most effective way to reduce this burden. TBE vaccines are available, but vaccines against LB are still in the phase of development. At the European level, TBE vaccines are likely under-administered to effectively prevent the disease. Cost-effectiveness of vaccination is a helpful tool in the decision making process to include novel vaccines in the national vaccination program or to extend current programs, and its role is only increasing. Cost-effectiveness studies on TBE vaccines have been performed in Slovenia, Sweden, Finland and Estonia so far. Cost-effectiveness studies with the novel vaccines against LB are expected to be performed in the near future.

Tick-borne diseases (TBDs) are one of the most rapidly expanding infectious diseases worldwide. Many new human tick-borne pathogens are discovered and several novel TBDs are recognized. Therefore, TBDs' burden may exceed the currently estimated burden.[1] TBDs are becoming an increasing public health concern globally.[1]

Increasing burden of TBDs shows that current available public health interventions and approaches are not effective enough. Vaccination could be a very effective and highly cost-effective intervention for preventing morbidity of the TBDs.[1,2] Whereas vaccines against Lyme borreliosis (LB) have not yet been developed, vaccines against tick-borne encephalitis (TBE) are available. Development of TBDs' vaccines faces numerous difficulties and challenges mainly due to diversity of human tick-borne pathogens. Antigenic variations of the LB spirochetes present an enormous obstacle in developing LB vaccines,

inclusive the differences between LB strains in Europe and the USA.[1] However, recently huge progress in vaccine development has been seen for LB. [3] At the moment, no human TBDs' vaccines are licensed in the USA [1]; however, vaccines against TBE are licensed for use in Europe and Russia. [4] In 1998, one of two developed monovalent vaccines, based on outer surface protein A (OspA), was licensed against LB for the use only in the USA.[5] In 2002, this vaccine was withdrawn from the USA market, mainly because of safety concerns related to potential occurrence of arthritis.[5] Currently, in Europe, huge efforts focus on development of a novel multivalent-based OspA vaccine. The risk for occurrence of potential arthritis with this novel vaccine seems eliminated.[3] At the moment, this novel vaccine potentially presents the most effective future protection against LB in the USA, Europe and Asia.[3] Other LB vaccines that include proteins

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such as OspB, OspC or DNA-binding protein HU-alpha are in different stages of development.[1] Also, various cocktails of several borrelia outer membrane and tick proteins are potential candidates for development of Lyme vaccines.[6] Tick proteins may be used for the development of an anti-tick vaccine for effective prevention not only against LB but also against other human TBDs in Europe. Notably, vaccination with an anti-tick vaccine could be a highly cost-effective public health intervention that can reduce the burden of TBDs and therefore their impact on the society.[2]

Cost-effectiveness is an important consideration nowadays prior to introduction of large-scale vaccination. Cost-effectiveness analysis (CEA) concerns an economic evaluation comparing costs and health outcomes, mostly expressed in quality-adjusted life years (QALYs), for vaccination versus no vaccination strategies. Results of CEAs are presented as incremental cost-effectiveness ratios (ICERs). The ICER is calculated as the difference in the cost of vaccination and no vaccination, divided by the difference in the health outcomes produced by vaccination and no vaccination. CEAs are supportive to government national committees advising on vaccination strategies, such as the Dutch Health Council, UK's Joint Committee on Vaccination & Immunization, the Belgium "Knowledge Center" and the "Ständigen Impfkommision" at the German Robert Koch Institute, on optimal use and reimbursement of new or existing vaccines.

TBE can affect the central nervous system, which may result in long-term/permanent neurological sequelae or even death.[4] At the European level, TBE presents an increasing public health concern with vaccination against TBE less widely used than possible to reduce the disease burden. Cost-effectiveness studies of TBE vaccines to support inclusion/expansion of TBE vaccination in national vaccination programs against TBE are needed. In 2012, the first study on the cost-effectiveness of two licensed Western European vaccines was published, using a Markov model.[7] The use of the Markov model for evaluating the cost-effectiveness of TBE vaccination was an innovation.[7] The Markov model was developed on the basis of the natural course of the disease.[7] Results were expressed in costs per QALY, showing that vaccination of adults aged 18–80 is cost-effective (inclusive boosters) from the view of the health care payer and even cost saving from the societal perspective in Slovenia.[7] The ICER for vaccination amounted to approximately €15,000–20,000 per QALY gained from the view of the health care payer.[7] The recognition of the importance of this study [7] can be seen when considering its impact. Firstly, in the Swedish county Sörmland, the County Council used this Markov model for their decision about TBE vaccination.[8] Results did not show favorable cost-effectiveness for all ages.[8,9] Secondly, in Finland, the cost-effectiveness study – using the same approach – showed that vaccination brings economic savings from the health care payer perspective with specific plausible assumptions on incidence of the disease, and respiratory paralysis and on

duration of treatment.[10] When the incidence of cases of respiratory paralysis would be reduced from 1/3 to 1/9 per year at the same incidence of the disease and duration of treatment, vaccination against TBE would still be cost-effective with an ICER at €16,000 per QALY gained from the health care perspective.[10] Also, for lowered assumptions on disease incidence, vaccination against TBE remained cost-effective.[10] Only at an incidence of the disease below 5/100,000, vaccination could become not cost-effective with an ICER higher than €100,000 per QALY gained.[10] Based on this cost-effectiveness study, the TBE immunization working group in Finland made a recommendation on vaccination against TBE.[10] Thirdly, an Estonian study [11] showed that vaccination of the whole population comes with an ICER of €61,000 per QALY gained, using a Markov model. Vaccination against TBE for the population ≥50 years is more cost-effective, with an ICER of €25,000 per QALY gained from the health care perspective.

Next to the cost-effectiveness of vaccination against TBE in Slovenia,[7] the burden for TBE was measured in disability-adjusted life years (DALYs) for the same country, using the updated DALYs methodology.[12,13] Notably, corrections for under-estimation were taken into account.[12,13] The burden of TBE was not previously expressed in DALYs. The burden model was developed based on the health outcomes of the natural course of the disease.[12,13] Results of the study showed that total DALYs amount to 3,450 [12,13] presenting a relative high burden as measured in DALYs compared with estimates for other infectious diseases from the Global Burden of Disease 2010 study for Slovenia. High TBE burden presents a public health challenge for more efficient policies and actions to reduce TBE in Slovenia, inclusive of an extended vaccination campaign in Slovenia. Taking into account the fact that in Slovenia and various similar countries, likely very low vaccination coverage exists,[14] ample room for improvement exists. Also, vaccination can add to a rising awareness about the disease that is proposed to also currently reduce the burden of TBE.[12] In Austria, it has been shown that extended TBE vaccination can be beneficial from both the health and economic perspectives.[15]

LB, the most common reported TBD, affects mostly the skin, joints, nervous system and heart.[16] Especially if LB is left untreated, it may lead to serious complications.[16] LB has even been suggested to potentially also be deadly.[1] LB is an increasing public health concern in many parts of the USA, across Europe and globally. Only in the USA, some studies on cost-effectiveness of vaccination with monovalent OspA vaccine against LB were performed, showing that the vaccine could be cost-effective at high risks of infection.[17–19] However, no cost-effectiveness studies with LB vaccines have been performed in Europe.[20]

CEA is crucial to support decision-making and guiding the choices to be made in the allocation of resources, as well as to determine strategic planning priorities. Further research on cost-effectiveness of vaccines against TBDs is needed, in particular regarding upcoming LB vaccines. Currently, such studies are

being planned. With TBDs being a serious public health concern, awareness of TBDs and increasing knowledge about TBDs among the general population remain important. Increasing investment in research, development and implementation of novel TBDs vaccines can crucially add to this, to further reduce the diseases' burden and ultimately lead to substantial health benefits and financial returns.

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